120 7/25/91 #5

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application

Bernauer et al.

Group: 126

Examiner: Reamer, J.

Serial No. 07/686,210, filed April 16, 1991

For: **CATECHOL DERIVATIVES**

INFORMATION DISCLOSURE STATEMENT

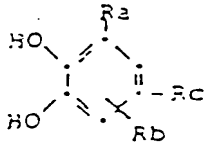
Nutley, New Jersey 07110
July 22, 1991

Honorable Commissioner of Patents and Trademarks
Washington D.C. 20231

S i r:

This statement is submitted pursuant to and in compliance with the provisions of 1.56, 1.97 and 1.98 of Title 37 of the Federal Regulations, as amended.

The claimed invention relates to a compound of the formula



Ia

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is halogen, nitro, cyano or the group $-(A)_n-(Q)_m-R'$ or $-(A)_n-Q-R^2$, A is vinylene optionally substituted by lower alkyl, n is the integer 0 or 1, m is the integer 0 or 1, R^1 is the group $-COR^3$, an aromatic carbocyclic group, or an aromatic or partially unsaturated heterocyclic group attached

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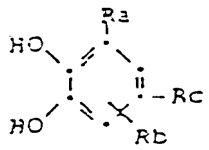
July 22, 1991

Ellen C Colletti

via a carbon atom, R^2 is hydrogen or an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue, R^3 is hydroxy, amino, an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue attached via an oxygen atom or an imino or lower alkylimino group or a saturated, N-containing heterocyclic group attached via a ring nitrogen atom, Q is the group -CO- or $>C=N(Z)_p-R^4$, Z is an oxygen atom or an imino group, p is the integer 0 or 1 and R^4 is hydrogen or a saturated or partially unsaturated lower hydrocarbon residue which is optionally substituted and which is optionally attached via a carbonyl group,

or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof.

In another aspect, the invention relates to pharmaceutical compositions comprising a compound of the formula



Ia

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is halogen, nitro, cyano or the group $-(A)_n-(Q)_m-R'$ or $-(A)_n-Q-R^2$, A is vinylene optionally substituted by lower alkyl, n is the integer 0 or 1, m is the integer 0 or 1, R^1 is the group $-COR^3$,

an aromatic carbocyclic group, or an aromatic or partially unsaturated heterocyclic group attached via a carbon atom, R^2 is hydrogen or an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue, R^3 is hydroxy, amino, an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue attached via an oxygen atom or an imino or lower alkylimino group or a saturated, N-containing heterocyclic group attached via a ring nitrogen atom, Q is the group -CO- or $>C=N(Z)_p-R^4$, Z is an oxygen atom or an imino group, p is the integer 0 or 1 and R^4 is hydrogen or a saturated or partially unsaturated lower hydrocarbon residue which is optionally substituted and which is optionally attached via a carbonyl group,

or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier material.

In connection with the foregoing invention, applicants wish to bring the following publications to the attention of the Patent and Trademark Office.

1. Kitahara, et al., U.S. Patent 4,622,066, November 11, 1986;
2. GB 967605, August 26, 1964;
3. Miyamoto et al., Chemical Abstracts, Vol. 99, 121998 (1983);
4. EP 79141, October 1982;
5. Backstrom et al., U.S. 4,963,590, October 16, 1990,

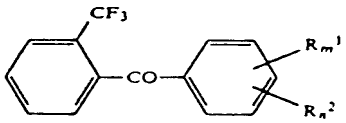
filed November 27, 1987; corresponding to New Zealand 222 729;

6. Hamazaki et al., U.S. Patent 4,124,726, November 7, 1987;
7. Gapinski, U.S. Patent 4,801,616, January 31, 1989;
8. Johnson et al., U.S. Patent 3,985,783, October 12, 1976;
9. Chemical Abstracts, Vol. 95, 135254t (1981);
10. British Patent Publication No. 2,038,819;
11. Nikadejevic, et al., Catechol-O-Methyl Transferase II. A New Class of Inhibitors of Catechol-O-Methyl Transferase, J. Pharmacol. Exp. Ther. 174, 83-93 (1970);
12. Fahn et al., Effect of Catechol-O-Methyl Transferase Inhibitor, U-0521 with Levodopa Administration, Biochem. Pharmacol. 28, 1221-1225 (1979);
13. Reches et al., Catechol-O-Methyl Transferase Inhibition by U-0521 Increase Striatal Utilization of Levodopa, Arch. Pharmacol. 320, 34-37 (1982);
14. Borchardt, et al., Catechol-O-Methyl Transferase, J. Med. Chem. 25, 258-263 (1982);
15. Borchardt and Huber, Catechol-O-Methyl Transferase, J. Med. Chem. 25, 321-323 (1982);
16. Borchardt and Huber, Function and Regulation of Monoamine Enzymes, Basic and Clinical Aspects, ed. E. Usdin, N. Weinder and M.B.H. Youdim, MacMillan Publishers, 1981, 657-664;
17. European Patent Publication No. 142,283, May 22, 1985;
18. Chemical Abstracts 92, 146461x (1980);
19. Chemical Abstracts 98, 50111f (1983);
20. Traxler and Ghisalba, A Genetic Approach to the Biosynthesis of the Rifamycin-Chromophore in Nocardia Mediterranei, J. Antibiotics 35(10), 1361-6 (1982);

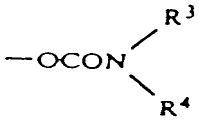
21. Chemical Abstracts Service, Registry Handbook 1965-1971, page 10666R; and

22. Britton et al., U. S. Patent No. 2,199,389, May 7, 1940.

Publication 1) discloses compounds of the formula



wherein R^1 is a group of the formula: -OM (in which M is hydrogen or alkali metal), lower alkoxy, lower acyloxy, a group of the formula:

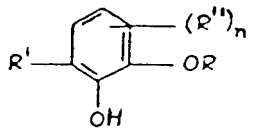


(in which R^3 and R^4 are same or different and hydrogen or lower alkyl) or a group of the formula: $-OCH_2COOR^5$ (in which R^5 is hydrogen, lower alkyl or alkali metal); R^2 is halogen, nitro, chlorosulfonyl, sulfo, trifluoromethyl or a group of the formula: $-SCF_2H$; and m and n, are each an integer of 1 to 4 provided that the sum of m and n is not more than 5.

With the aid of applicants' disclosure, Publication 1) arguably generically discloses a compound of formula I wherein Ra is nitro, Rb is hydrogen and Rc is 2-(trifluoromethyl) benzoyl which is stated to have selective herbicidal activity

on grasses, not crops.

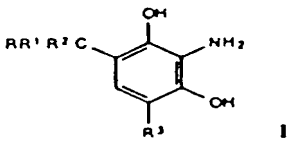
Publication 2) relates to a process for the production of orthodihydroxy benzene derivatives of the formula



where R represents a hydrogen atom, R^1 represents a hydrogen or halogen atom or an alkyl, alkenyl or alkoxy radical of from 1 to 4 carbon atoms, R^{11} represents a halogen atom or a nitro, sulpho, sulphino, mercapto or hydroxyl group or a hydrocarbon or oxygenated hydrocarbon group containing from 1 to 18 carbon atoms, or an amino methyl, sulphino methyl, mercapto methyl or sulphonyl methyl group and n is 0 or an integer from 1 to 3.

Publication 2) arguably generically discloses a compound of formula I of the invention wherein Ra is nitro, Rc is nitro or halogen and Rb is hydrogen.

Publication 3) discloses compounds of the formula



I

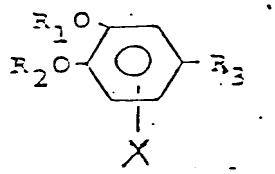
R=alkyl, (un)substituted Ph, aralkyl; R^1=H,R^2=OH, alkoxy; R^1R^2=O; R^3=H,halogen, alkyl, SPh,

which inhibit 5-lipoxygenase.

In addition, Publication 3) discloses the intermediate compound, $2,4,3-(HO)_2(O_2N)C_6H_2COPh$, which arguably are "positional isomers" of the claimed compounds.

Publication 4), referred to in Publication 3), discloses pharmaceutical compositions for treating bronchial or lung and tracheal allergic diseases and inflammations induced by prostaglandin comprising a compound of formula I above.

Publication 5) discloses allegedly pharmacologically active catechol derivatives of the formula



wherein R_1 and R_2 independently represent hydrogen, alkyl, acyl or optionally substituted aroyl, lower alkylsulphonyl or alkylcarbamoyl or taken together form a lower alkylidene or cycloalkylidene group; X represents halogen, nitro, cyano, lower alkylsulphonyl, sulphonamido, aldehyde, carboxyl or trifluoromethyl in position 5 or 6 and R_3 represents hydrogen, halogen, hydroxyalkyl, amino, nitro, cyano, trifluoromethyl, lower alkylsulfonyl, sulfonamide, aldehyde, alkylcarbonyl, aralkylidonecarbonyl or carboxyl or a group selected from $-CH=C(R_4)R_5$ and $-CH_2CH(R_4)R_5$ wherein R_4

represents hydrogen, alkyl, cyano, carboxyl or acyl and R_5 represents hydrogen, cyano, carboxyl, alkoxycarbonyl, carboxyalkenyl, nitro, acyl, hydroxyalkyl, carboxyalkyl or one of the optionally substituted groups; aroyl or heteroaroyl; or R_4 and R_5 together form a five to seven membered, optionally substituted cycloalkanone ring; $-(CO)_n(CH_2)_m-COR$, wherein n is 0 or 1, and m is 0-7 and R represents hydroxy, alkyl, carboxyalkyl, optionally substituted alkene, alkoxy or optionally substituted amino; $-CON(R_8)R_9$ wherein R_8 and R_9 independently represent hydrogen or one of the following optionally substituted groups; alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, or together form an optionally substituted piperidyl group; and $-NH-CO-R_{10}$ wherein R_{10} represents a substituted alkyl group.

In another aspect, publication 5) discloses pharmaceutical compositions and methods for inhibiting catechol-O-methyl transferase and for treating Parkinson's disease, heart failure, depression and hypertension comprising a compound of formula I.

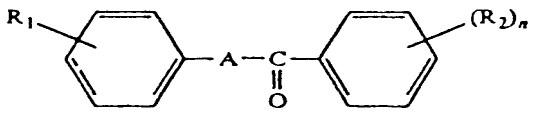
While this publication may be pertinent to the claimed invention and the Examiner may wish to consider it, the publication is not available as a prior art reference against the instant application. As is evident, the filing date of US 4,963,590, is antedated by the filing date of applicants' U.S. priority application, Serial No. 07/022,891, namely, March 6, 1987.

Applicants are not aware of any foreign patents

corresponding to U.S. 4,963,590, that issued prior to the filing date of applicants' U.S. priority application.

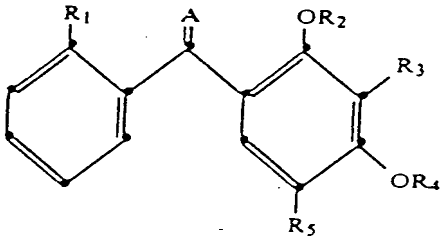
Furthermore, U.S. 4,963,590 does not claim subject matter which overlaps with that of the instant application.

Publication 6) relates to compounds of the formula

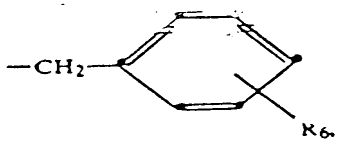


wherein R_1 represents hydrogen, halogen, hydroxy, C_{1-8} alkyl or C_{1-8} alkoxy,
R_2 represents hydrogen, halogen, hydroxy, vinyl, C_{1-8} alkyl or C_{1-8} alkoxy,
A represents carbonyl, methylene or a single bond, and
n is an integer of 1 to 4.

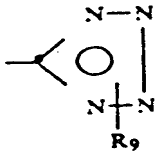
Publication 7) discloses diphenylmethane compounds of the formula



and pharmaceutically acceptable salts thereof wherein
R_1 is -OH, -O-(C_1-C_4 alkyl), halo, or -OCO(C_1-C_4 alkyl);
A is O, CH_2, or CH(C_1-C_4 alkyl);
R_2 is hydrogen or C_1-C_4 alkyl;
R_3 is C_1-C_4 alkyl or C_2-C_4 alkenyl;
R_3 is -H, C_1-C_4 alkyl, -CO(C_1-C_4 alkyl) -alk-R_6, or

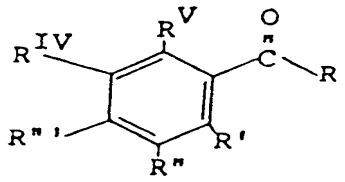


or R_3 and R_4 when taken with the oxygen atom to which R_4 is attached are —$CH_2CH(CH_3)O$—;
R_5 is —H or C_1–C_4 alkyl; and
R_6 is —CN, —COOH, —COO(C_1–C_4 alkyl), —$CONR_7R_8$, or



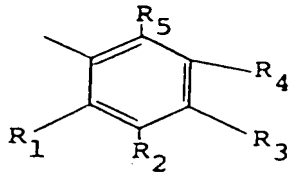
where
R_7 and R_8 are each independently hydrogen or C_1–C_3 alkyl,
R_9 is hydrogen or C_1–C_4 alkyl, and "alk" is a divalent organic radical derived from a C_1–C_8 aliphatic hydrocarbon.

Publication 8) relates to a process for ring acylation of phenols to obtain compounds of the formula



I

wherein R′, R″, R‴, R^{IV} and R^{V} are independently selected from the group consisting of hydrogen, hydroxy, (C_{1-3})-alkyl, (C_{1-3})-alkoxy and carbo-(C_{1-3})-alkoxy, with the proviso that at least one of R′ and R‴ is hydroxy; R is a (C_{1-3})-alkyl radical or the group



wherein the substituents R_1 through R_5 are independently selected from hydrogen, (C_{1-3})-alkyl, (C_{1-3})-alkoxy, benzyloxy, hydroxy, halo, nitro, cyano and amino.

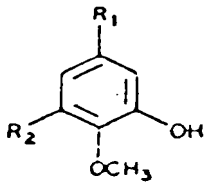
Publications 9) and 10) disclose 3,5-dinitro-1,2-dihydroxybenzene.

Publication 11) relates to, for example, 3-methoxy-4,5-dihydroxybenzoic acid and the like (see pages 87-88).

Publication 12) relates to a study of the effect of 3′,4′-dihydroxy-2-methyl-propriophenone, a catechol-O-methyl transferase inhibitor (COMT), with levodopa administration.

Publication 13) relates to a study of the effect of COMT inhibition by 3′,4′-dihydroxy-2-methyl propiophenone on Dopa metabolism in rat striatum.

Publication 14) relates to a study of 5-substituted-3-hydroxy-4-methoxybenzoic acids and 5-substituted-3-hydroxy-4-methoxybenzaldehydes of the formulas

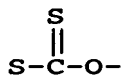


	R_1	R_2		R_1	R_2
1	CO_2H	H	10	CHO	H
2	CO_2H	OCH_3	11	CHO	F
3	CO_2H	Cl	12	CHO	Cl
4	CO_2H	Br	13	CHO	Br
5	CO_2H	I	14	CHO	I
6	CO_2H	NO_2	15	CHO	NO_2
7	CO_2H	NH_2	16	CHO	OH
8	CO_2H	$N(CH_3)_2$	17	CHO	SC(S)OEt
9	CO_2H	CN			

as potential inhibitors of COMT.

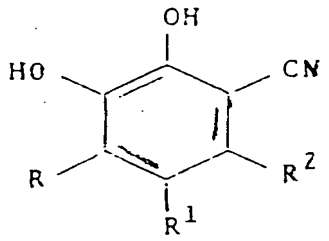
Publication 15) relates, for example, to 5-hydroxy-3-mercapto-4-methoxybenzoic acid.

Publication 16) discloses 3-substituted-4-methoxy-5-hydroxybenzoic acid. The substituents may be, for example, OCH_3, Cl, Br, I, NO_2, NH_2, $N(CH_3)_2$, CN, SH. Also disclosed are 3-substituted-4-methoxy-5-hydroxybenzaldehyde, the substituents may be, for example, F, Cl, Br, I, NO_2, OH,



Publication 17) describes phenylethylamines, having, for example, hydroxy, halogen and nitro substituents.

Publication 18) discloses 3-cyanocatechol derivatives of the formula

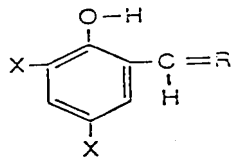


wherein R, R^1 and R^2 can be, for example, H,H,H; H,MeO,H; Me,H,H; Me,Me,H; H, Cl, H; Cl,Cl,H; Br,H,H; H,H,I.

Publications 19) and 20) disclose, among others, the compounds 3-nitro-4,5-dihydroxybenzoic acid and 3-amino-4,5-dihydroxybenzoic acid.

Publication 21) discloses, among others, the compound 5-formyl-2,3-dihydroxybenzonitrile.

Publication 22) discloses compounds of the formula



wherein one x is a nitro group, the other x is hydrogen or a nitro group, and R is an organic residue containing a double bond in conjugated relationship to that existing between R and the

side-chain carbon atom attached to the benzene nucleus.

The Examiner is respectfully requested to consider the above publications in connection with the examination of the captioned application.

The Examiner is hereby authorized to call the undersigned attorney of record "collect" on any matter connected with this application. The telephone number is Area Code (201) 235-5171. In the absence of the undersigned attorney of record, the call will be accepted by another attorney empowered in this application.

Respectfully submitted,

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